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Synthesis of [9]Heterophanes from 2-Cyclododecenone

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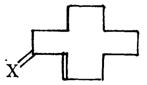
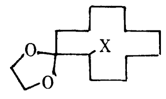
[9](3,5)Pyrazolophane (V) and 11-methyl[9](2,4)furanophane (IX) were prepared from 2-cyclododecenone (I) and their spectral properties were discussed. A new route to I from cyclododecanone is described.

The unusual properties of cyclophanes have received considerable attention. In particular, NMR investigations of the conformational changes have been conducted extensively.[1] Interest has also been focused on their heteroaromatic analogs (heterophanes[2,3]), as two natural products, muscopyridine[4] and metacycloprodigiosin,[5] were shown to have [10](2,6)pyridinophane and [9](2,4)pyrrolophane structure, respectively. In continuation of studies on the heterophanes,[2,6] we carried out the synthesis of [9]heterophanes from 2-cyclododecenone (I).[*1]

cis- and *trans*-2-cyclododecenone (I) were prepared from cyclododecene oxide.[8] An alternative route to I has been explored in this study starting from commercially available cyclododecanone. Bromination of cyclododecanone ethylene acetal (II) followed by dehydrobromination of the resulting III with potassium *t*-butoxide in dimethyl sulfoxide afforded IV, which was in turn hydrolyzed to I (*cis* : *trans* = 1 : 4). The stereoisomeric mixture of I was subjected to further reactions without separating the components. The spectral data of these compounds supported their assigned structures.



I: X=O
IV: X=–OCH$_2$CH$_2$O–



II: X=H
III: X=Br

[9](3,5)Pyrazolophane (V) was synthesized as follows. Treatment of I with hydrazine hydrate in ethanol gave the corresponding pyrazoline (VI) which was a distillable but quite labile solid (MS, m/e 194 (M^+)). Freshly distilled VI was admixed with powdered sulfur and dehydrogenated at 200—220°C to afford pyrazolophane V. Compound V showed IR absorptions characteristic of the pyrazole ring (3200, 3025 and 1580 cm^{-1}). The NMR spectrum of V (Fig. 1) was consistent with the assigned structure (*vide infra*).

1,2-Addition of lithium acetylide to I gave 1-ethynyl-2-cyclododecen-1-ol (VII) whose spectral

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[1] F. Vögtle, *Chem. Ber.*, **102**, 3077 (1969) and references cited therein.

[2] H. Nozaki, T. Koyama and T. Mori, *Tetrahedron*, **25**, 5357 (1969).

[3] In agreement with Vögtle's proposal, we will call this kind of compound "heterophane" rather than "heterocyclophane." See F. Vögtle and P. Neumann, *Tetrahedron Lett.*, **1969**, 5329.

[4] K. Biemann, G. Büchi and B. H. Walder, *J. Amer. Chem. Soc.*, **79**, 5558 (1957).

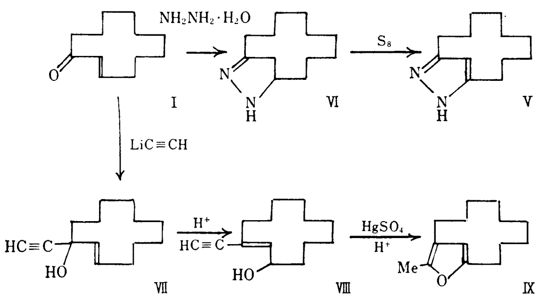
[5] H. H. Wasserman, G. C. Rodgers and D. D. Keith, *ibid.*, **91**, 1263 (1969); H. H. Wasserman, D. D. Keith and J. Nadelson, *ibid.*, **91**, 1264 (1969).

[6] H. Nozaki, S. Fujita and T. Mori, This Bulletin, **42**, 1163 (1969).

[*1] When the present investigation of [9]heterophane was almost completed, Bradamante *et al.* reported a different approach to several [9]heterophanes.[7] This communication prompted us to report independent results obtained at present by using I as a starting material.

[7] S. Bradamante, R. Fusco, A. Marchesini and G. Pagani, *Tetrahedron Lett.*, **1970**, 11.

[8] H. Nozaki, T. Mori and R. Noyori, *Tetrahedron*, **22**, 1207 (1966).



data were consistent with the assigned structure. Acid catalyzed isomerization of VII yielded 3-ethynyl-2-cyclododecen-1-ol (VIII). Subsequent treatment of VIII with mercuric sulfate under acidic condition resulted in cycloaddition of hydroxyl on ethynyl group to afford 11-methyl [9](2,4)furanophane (IX) which displayed IR absorptions due to the furan ring (3100, 1579 and 798 cm^{-1}).

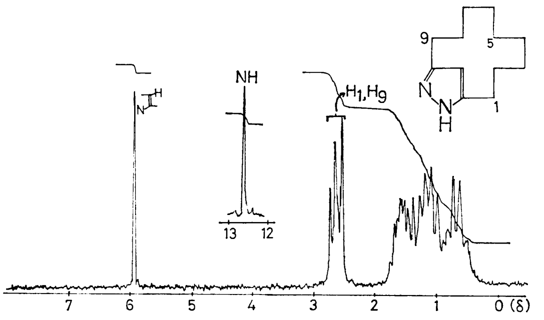


Fig. 1. The NMR spectrum of V (CCl$_4$, at 24°C, 60 MHz).

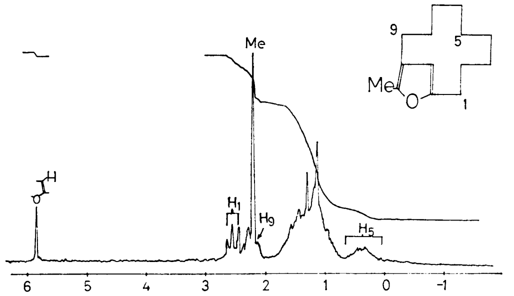


Fig. 2. The NMR spectrum of IX (CCl$_4$, at 60 MHz, 24°C).

The NMR spectra of the heterophanes prepared are shown in Figs. 1 and 2. Each nonamethylene chain should be flexible at room temperature, since the signal due to C$_1$ and C$_9$ protons can be approximately regarded as a triplet. Several methylene protons of chains were magnetically shielded as compared with the usual paraffinic methylene. The shielding effect may be ascribed to the diamagnetic ring current of pyrazole and furan ring. In particular, one of IX (*cf.* Fig. 2) made the signal of one methylene group separate from other peaks (δ 0.6—0.1 in CCl$_4$ and in CS$_2$). It is tentatively assigned to C$_5$ protons on the basis of conformational inspection by the Dreiding model. The position of the signal was dependent on temperature and shifted to a much higher field (δ 0.0—−0.7, one proton) upon cooling to −72.5°C (Fig. 3). Probably, at this temperature the nonamethylene chain of IX is fixed to some extent and one of the C$_5$ methylene protons is forced close to the π-cloud of the furan ring. Since the UV spectrum of furanophane IX shows a considerable red shift as compared with 2,5-dimethylfuran (λ_{max} 218.5 nm), the furan ring of IX appears to suffer a distortion from coplanarity⁹⁾ similar to that of [8](2,5)furanophane.²⁾

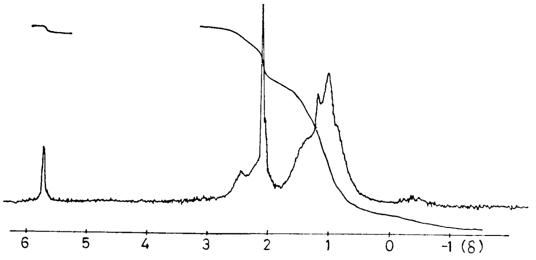


Fig. 3. The NMR spectrum of IX (CS$_2$, at 60 MHz, −72.5°C).

Experimental

All melting points are uncorrected. NMR data were obtained on a JEOL C-60-H spectrometer. Mass spectra were taken on a Hitachi RMS-4 spectrometer.

Cyclododecanone Ethylene Acetal (II). A solution of cyclododecanone (150 g, 0.82 mol), ethylene glycol (60 g, 0.97 mol) and *p*-toluenesulfonic acid (catalytic amount) in dry benzene (700 m*l*) was heated to reflux for 110 hr using a Dean-Stark condenser. The mixture was washed with water, dried over sodium sulfate and concentrated *in vacuo*. Distillation of the crude crystals through Vigreux column gave II (155 g, 84%) as pale yellow crystals, bp 104—105°C/0.2 mmHg, mp 68—71°C (ethyl acetate) (lit,¹⁰⁾ bp 125—130°C/3 mmHg, mp 70°C). IR (Nujol): 2948, 1480, 1390, 1231, 1124, 1064, 996, 957 and 875 cm^{-1}.

2-Bromocyclododecanone Ethylene Acetal (III). To a solution of II (22.6 g, 0.10 mol) in dry ether (70 m*l*) bromine (18.0 g, 0.11 mol) was added dropwise for 3 hr with vigorous stirring. The reaction mixture was neutralized with monosodium ethylene glycolate. After the ethereal layer was separated, the aqueous layer was thoroughly extracted with ether. The combined extracts were washed with water, dried over sodium sulfate and concentrated *in vacuo*. Fractional distillation of the residue yielded III (24.0 g, 79%), bp 120—124°C/0.08 mmHg, mp 72.9—73.6°C (ethyl acetate). IR

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9) B. H. Smith, "Bridged Aromatic Compounds," Academic Press, New York, N. Y. (1964).

10) Haarmann and Reimer G. m. b. H., Fr. 1393647 (1965); *Chem. Abstr.*, 6886 (1965).

(Nujol): 2930, 2860, 1470, 1382, 1223, 1144, 1128, 1064, 984, 957 and 880 cm^{-1}. NMR ($\mathrm{CCl_4}$): δ 4.4—4.7 (4H, m, $\mathrm{-OCH_2CH_2O-}$) and 2.3—1.1 (21H, m).

Found: C, 55.0; H, 8.3%. Calcd for $\mathrm{C_{14}H_{25}O_2Br}$: C, 55.1; H, 8.2%.

2-Cyclododecenone Ethylene Acetal (IV). A mixture of III (16.7 g, 55 mmol), potassium *t*-butoxide (12.3 g, 110 mmol) and dimethyl sulfoxide (70 m*l*) was mechanically stirred for 5 hr at 90°C under nitrogen atmosphere. The mixture was diluted with water and extracted with ether. The extracts were washed with water, dried (sodium sulfate) and concentrated *in vacuo*. Distillation of the residue gave IV (8.6 g, 70%), bp 150—153°C/5 mmHg. IR (neat): 3017, 2922, 1667, 1465, 1448, 1168, 1135, 1038, 983 and 946 cm^{-1}. NMR ($\mathrm{CCl_4}$): δ 5.99—5.08 (2H, m, olefinic), 3.75 (4H, s, $\mathrm{-OCH_2CH_2O-}$) and 2.5—1.2 (18H, m).

Found: C, 74.5; H, 10.6%. Calcd for $\mathrm{C_{14}H_{24}O_2}$: C, 75.0; H, 10.8%.

2-Cyclododecenone (I). Hydrolysis of IV with dilute sulfuric acid gave a mixture of *cis*- and *trans*-2-cyclododecenone (*cis* : *trans*=1 : 4) in 74% yield, bp 127—134°C/7 mmHg (lit,[8] 95—105°C/3 mmHg).

3,5-Nonamethylene-2-pyrazoline (VI). A solution of I (1.85 g, 10.3 mmol) and hydrazine hydrate (80%, 1.37 g) in ethanol (30 m*l*) was heated to reflux for 1.5 hr. After concentration, the residue was distilled *in vacuo* to yield VI, as a white solid (1.10 g, 55%), bp 95—98°C/0.07 mmHg. The solid was so labile as to turn into a viscous yellow oil on exposure to air. The IR spectrum(neat) showed prominent peaks at 3302, 2902, 1624, 1471, 1293, 845 and 812 cm^{-1}, and MS exhibited a molecular ion peak at *m/e* 194.

[9](3,5)Pyrazolophane (V). Freshly distilled VI (1.10 g, 5.7 mmol) was admixed with powdered sulfur (0.18 g, 5.7 mmol) and heated at 200—220°C under nitrogen atmosphere for 2 hr. After the evolution of hydrogen sulfide had ceased, the crude product was subjected to separation on a silica gel column to afford crystalline V (0.77 g, 71%), mp 109—109.7°C (*n*-hexane). IR (Nujol): 3200, 3130, 3100, 3025, 2922, 2850, 1580, 1460, 1371, 1148 and 782 cm^{-1}. $\lambda_{\max}$ (EtOH): 207 nm (log ε 4.54). MS *m/e* (intensity): 192 (26), 177 (2), 163 (11), 149 (29), 135 (10), 124 (18), 110 (22), 109 (23) and 95 (100). The NMR is shown in Fig. 1.

Found: C, 75.1; H, 10.5%. Calcd for $\mathrm{C_{12}H_{20}N_2}$: C, 75.0; H, 10.5%.

1-Ethynyl-2-cyclododecen-1-ol (VII). To a freshly prepared solution of lithium acetylide (from 0.13 g lithium) in liquid ammonia[11] a solution of I (2.41 g, 13 mmol) in dry ether (10 m*l*) was added dropwise in 10 min and mechanical stirring was continued for 2 hr at −35°C. The reaction mixture was treated with ammonium chloride (1.0 g) and allowed to stand overnight at room temperature. The residue was mixed with water and extracted with ether. The combined extracts were washed with water, dried over sodium sulfate, concentrated under reduced pressure and distilled to yield VII (1.41 g, 51%), bp 85—91°C/0.06 mmHg. IR (neat): 3425, 3332, 2120, 1625, 1464, 1448, 1111, 1015, and 978 cm^{-1}. NMR ($\mathrm{CCl_4}$): δ 2.40 (1H, s, OH), 2.80 (1H, s, C≡CH), 5.75 (2H, m) and 2.45—0.77 (18H, m).

Found: C, 81.3; H, 10.7%. Calcd for $\mathrm{C_{14}H_{22}O}$: C, 81.5; H, 10.8%.

3-Ethynyl-2-cyclododecen-1-ol (VIII). A solution of VII (1.27 g, 6.2 mmol) in tetrahydrofuran (15 m*l*) and 4% sulfuric acid (10 m*l*) was magnetically stirred at 100°C for 45 min under nitrogen atmosphere. After evaporation of tetrahydrofuran, the residual aqueous layer was extracted with ether, washed with water, dried over sodium sulfate and concentrated *in vacuo*. Distillation of the residue afforded VIII (1.10 g, 87%) as a highly viscous oil, bp 90—105°C/0.06 mmHg. IR (neat): 3372, 3325, 2079, 1621, 1464, 1447, 1111, 1034, 1009, 979 and 847 cm^{-1}. NMR ($\mathrm{CCl_4}$): δ 5.73 (1H, d, *J*=9 Hz, C=CH), 3.94 (1H, s, OH), 3.26—2.88 (1H, m), 3.14 (1H, s, C≡CH) and 2.58—0.61 (18H, m).

Found: C, 81.3; H, 10.7%. Calcd for $\mathrm{C_{14}H_{22}O}$: C, 81.5; H, 10.8%.

11-Methyl[9](2,4)furanophane (IX). A solution of VIII (0.25 g, 1.2 mmol), mercuric sulfate (92 mg) and 2% sulfuric acid (10 m*l*) in dioxane (15 m*l*) was heated to reflux at 100°C for 1.5 hr under nitrogen atmosphere. The mixture was neutralized with aqueous sodium hydrogen carbonate and extracted with ether. The ether extracts were washed with water, dried over sodium sulfate and concentrated *in vacuo*. The crude mixture was purified through a silica gel column and distilled under reduced pressure to give IX (0.045 g, 18%), bp 72—75°C/1.5 mmHg. IR (neat): 3100, 2927, 2862, 1637, 1579, 1467, 1346, 1217, 1191, 997, 929 and 798 cm^{-1}. $\lambda_{\max}$ (EtOH): 225 nm (log ε 2.68). MS *m/e* (intensity): 206 (49), 191 (16), 177 (11), 163 (35), 149 (34), 135 (48), 121 (60) and 108 (100).

Found: C, 81.7; H, 10.6%. Calcd for $\mathrm{C_{14}H_{22}O}$: C, 81.5; H, 10.8%.

The NMR spectra at room temperature and at −72.5°C are shown in Figs. 2 and 3, respectively.

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[11] R. A. Raphael, "Acetylenic Compounds in Organic Syntheses," p. 193, Academic Press, New York, N. Y. (1955).